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(54) EP2-RECEPTOR AGONISTS AS AGENTS FOR LOWERING INTRAOCULAR PRESSURE

EP2-REZEPTORAGONISTEN ALS MITTEL ZUR SENKUNG DES AUGENINNENDRUCKS

AGONISTES DE RECEPTEUR EP2 UTILISES COMME AGENTS FAISANT BAISSER LA TENSION INTRAOCULAIRE

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(56) References cited:
US-A- 4 599 353

- **JOURNAL OF OCULAR PHARMACOLOGY, vol. 10,no. 1, 1994 pages 177-193, D.F.WOODWARD ET AL. 'Studies on the ocular hypotensive effects of prostaglandin F2alpha ester prodrugs and receptor selective prostaglandin analogs'**

EP 0 789 687 B1

Description

Field of the Invention

[0001] The present invention relates to the use for the manufacture of a medicament of EP_2 receptor agonists to lower the intraocular pressure of mammals and thus are useful in treating glaucoma. In particular, (±) trans-2-[-4(1-hydroxyhexyl) phenyl]-5-oxocyclopentaneheptanoicacid, and ester and unsaturated derivatives thereof, are effective for the management of glaucoma.

Background of the Invention

[0002] Ocular hypotensive agents are useful in the treatment of a number of various ocular hypertensive conditions, such as post-surgical and post-laser trabeculectomy ocular hypertensive episodes, glaucoma, and as presurgical adjuncts.

[0003] Glaucoma is a disease of the eye characterized by increased intraocular pressure. On the basis of its etiology, glaucoma has been classified as primary or secondary. For example, primary glaucoma in adults (congenital glaucoma) may be either open-angle or acute or chronic angle-closure. Secondary glaucoma results from pre-existing ocular diseases such as uveitis, intraocular tumor or an enlarged cataract.

[0004] The underlying causes of primary glaucoma are not yet known. The increased intraocular tension is due to the obstruction of aqueous humor outflow. In chronic open-angle glaucoma, the anterior chamber and its anatomic structures appear normal, but drainage of the aqueous humor is impeded. In acute or chronic angle-closure glaucoma, the anterior chamber is shallow, the filtration angle is narrowed, and the iris may obstruct the trabecular meshwork at the entrance of the canal of Schlemm. Dilation of the pupil may push the root of the iris forward against the angle, and may produce pupillary block and thus precipitate an acute attack. Eyes with narrow anterior chamber angles are predisposed to acute angle-closure glaucoma attacks of various degrees of severity.

[0005] Secondary glaucoma is caused by any interference with the flow of aqueous humor from the posterior chamber into the anterior chamber and subsequently, into the canal of Schlemm. Inflammatory disease of the anterior segment may prevent aqueous escape by causing complete posterior synechia in iris bombe and may plug the drainage channel with exudates. Other common causes are intraocular tumors, enlarged cataracts, central retinal vein occlusion, trauma to the eye, operative procedures and intraocular hemorrhage.

[0006] Considering all types together, glaucoma occurs in about 2% of all persons over the age of 40 and may be asymptotic for years before progressing to rapid loss of vision. In cases where surgery is not indicated, topical β - adrenoreceptor antagonists have traditionally been the drugs of choice for treating glaucoma.

[0007] Prostaglandins were earlier regarded as potent ocular hypertensives; however, evidence accumulated in the last two decades shows that some prostaglandins are highly effective ocular hypotensive agents and are ideally suited for the longterm medical management of glaucoma. (See, for example, Starr, M.S. Exp. Eye Res. 1971, 11, pp. 170-177; Bito, L. Z. Biological Protection with Prostaglandins Cohen, M. M., ed., Boca Raton, Fla, CRC Press Inc., 1985, pp. 231-252; and Bito, L. Z., Applied Pharmacology in the Medical Treatment of Glaucomas Drance, S. M. and Neufeld, A. H. eds., New York, Grune & Stratton, 1984, pp. 477-505). Such prostaglandins include $PGF_{2\alpha}$, $PGF_{1\alpha}$, PGE_2, and certain lipid-soluble esters, such as C_1 to C_5 alkyl esters, e.g. 1-isopropyl ester, of such compounds.

[0008] In the United States Patent No. 4,599,353 certain prostaglandins, in particular PGE_2 and $PGF_{2\alpha}$ and the C_1 to C_5 alkyl esters of the latter compound, were reported to possess ocular hypotensive activity and were recommended for use in glaucoma management.

[0009] Although the precise mechanism is not yet known, recent experimental results indicate that the prostaglandininduced reduction in intraocular pressure results from increased uveoscleral outflow [Nilsson et al., Invest. Ophthalmol. Vis. Sci. 28(suppl), 284 (1987)].

[0010] The isopropyl ester of $PGF_{2\alpha}$ has been shown to have significantly greater hypotensive potency than the parent compound, which was attributed to its more effective penetration through the cornea. In 1987 this compound was described as "the most potent ocular hypotensive agent ever reported." [See, for example, Bito, L. Z., Arch, Ophthalmol, 105, 1036 (1987), and Siebold et al., Prodrug 5, 3 (1989)].

[0011] Whereas prostaglandins appear to be devoid of significant intraocular side effects, ocular surface (conjunctival) hyperemia and foreign-body sensation have been consistently associated with the topical ocular use of such compounds, in particular $PGF_{2\alpha}$ and its prodrugs, e.g. its 1-isopropyl ester, in humans. The clinical potential of prostaglandins in the management of conditions associated with increased ocular pressure, e.g. glaucoma, is greatly limited by these side effects.

[0012] Certain phenyl and phenoxy mono, tri and tetra nor prostaglandins and their 1-esters are disclosed in European Patent Application 0,364,417 as useful in the treatment of glaucoma or ocular hypertension.

[0013] In a series of co-pending United States patent applications assigned to Allergan, Inc. prostaglandin esters

with increased ocular hypotensive activity accompanied with no or substantially reduced side-effects are disclosed.

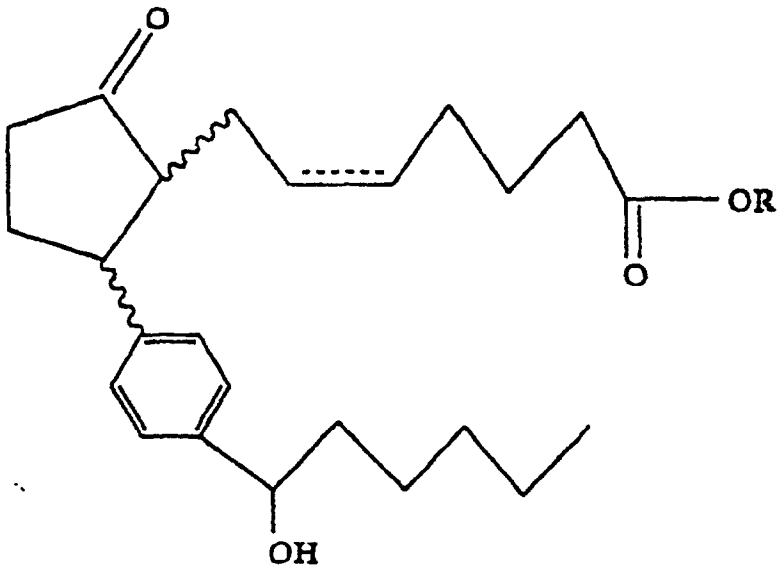
[0014] See the co-pending patent applications USSN No. 385,645 filed 27 July 1990, now U.S. Patent No. 4,494,274; 584,370 which is a continuation of USSN No. 386,312, and 585,284, now U.S. Patent No. 5,034,413 which is a continuation of USSN 386,834, where the parent applications were filed on 27 July 1989.

[0015] Finally, certain EP_2-receptor agonists are disclosed in Nials et al, Cardiovascular Drug Reviews, Vol. 11, No. 2, pp. 165-179, Coleman et al, Comprehensive Medicinal Chemistry, Vol. 3, pp. 643-714, 1990 and Woodward et al, Prostaglandins, pp. 371-383, 1993.

Summary of the Invention

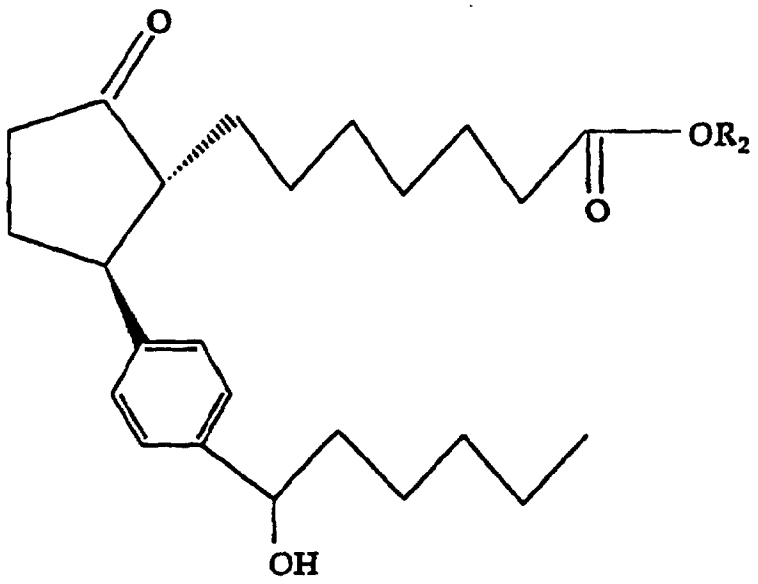
[0016] We have found that certain EP_2-receptor agonists are potent ocular hypotensive agents. We have further found that (±) trans-2-[-4(1-hydroxyhexyl) phenyl]-5-oxocyclopentaneheptanoicacid, and ester and unsaturated derivatives thereof, are especially useful in the treatment of glaucoma and surprisingly, cause no or significantly lower ocular surface hyperemia than the other compounds that are useful in lowering intraocular pressure, e.g. $PGF_{2\alpha}$ and lower alkyl esters thereof.

[0017] The present invention relates to a compound for use in treating ocular hypertension, which compound is represented by the formula I



wherein, the wavy bands indicate the α or β configuration, R is a saturated or unsaturated acyclic hydrocarbon group having from 1 to 20 carbon atoms, or $-(CH_2)_mR_1$ wherein m is 0-10, and R_1 is an aliphatic ring having from 3 to 7 carbon atoms, or an aryl or heteroaryl ring having from 4 to 10 carbon atoms, and wherein the heteroatom is selected from N, O and S; e.g. R_1 may be cyclohexyl, phenyl, thienyl, pyridyl or furanyl, or a pharmaceutically acceptable salt thereof and the dashed bond represents either a single or double bond which may be in the cis or trans position. Preferably R_1 is lower alkyl.

[0018] More preferably the compounds for use according to the present invention are represented by the formula II



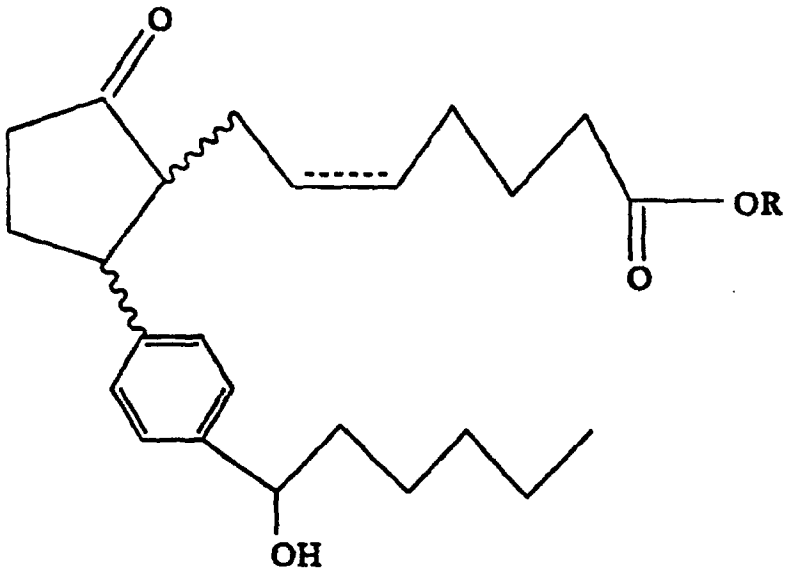
wherein R_2 is a lower alkyl radical and the other symbols are as defined above.

[0019] In a further aspect, the present invention relates to pharmaceutical compositions comprising a therapeutically effective amount of a compound of formulae (I) or (II) wherein the symbols have the above meanings, or a pharmaceutically acceptable salt thereof in admixture with a non-toxic, pharmaceutically acceptable liquid vehicle.

[0020] In a still further aspect, the present invention relates to certain (±) trans-2-[-4(1-hydroxyhexyl) phenyl]-5-oxocyclopentaneheptanoicacid, and ester and unsaturated derivatives thereof, of the above formulae, wherein the substituents and symbols are as defined hereinabove, or a pharmaceutically acceptable salt of such compounds.

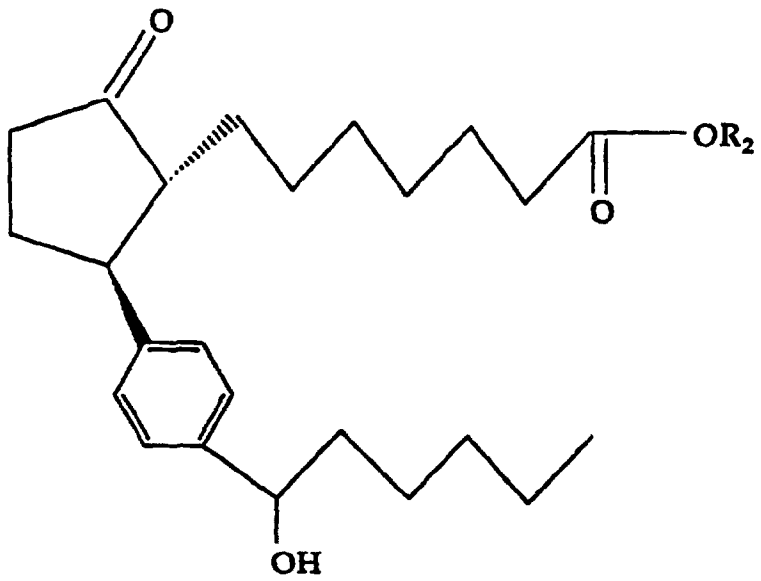
Detailed Description of the Invention

[0021] The present invention relates to (±) trans-2-[-4(1-hydroxyhexyl) phenyl]-5-oxocyclopentaneheptanoic- acid, and ester and unsaturated derivatives thereof, for use as ocular hypotensives. These therapeutic agents are represented by compounds having the formula I



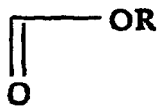
as defined above. The preferred compounds used in accordance with the present invention are encompassed by the

following structural formula II



wherein R_2 is a lower alkyl radical.

[0022] In all of the above formulae, as well as in those provided hereinafter, the straight lines represent bonds. Where there is no symbol for the atoms between the bonds, the appropriate carbon-containing radical is to be inferred. For example in formula I, the radical between the cyclopentyl ring and the



radical is a polymethylene (CH_2) radical, i.e. a hexylenyl radical. The dotted lines on the bond between carbons 5 and 6 (C-5), indicate a single or a double bond which can be in the cis or trans configuration. The radical adjacent the double bond is a CH radical. If two solid lines are used that indicates a specific configuration for that double bond. Hatched lines at positions C-9 and C-11 indicate the α configuration. If one were to draw the β configuration, a solid triangular line would be used.

[0023] In the compounds used in accordance with the present invention, compounds having the C-9 or C-11 substituents in the α or β configuration are contemplated. As hereinabove mentioned, in all formulas provided herein broken line attachments to the cyclopentane ring indicate substituents in the α configuration. Thickened solid line attachments to the cyclopentane ring indicate substituents in the β configuration.

[0024] For the purpose of this invention, unless further limited, the term "alkyl" refers to alkyl groups having from one to ten carbon atoms and includes "lower alkyl" radicals having from one to five carbon atoms, the term "cycloalkyl" refers to cycloalkyl groups having from three to seven carbon atoms, the term "aryl" refers to aryl groups having from four to ten carbon atoms. The term "saturated or unsaturated acyclic hydrocarbon group" is used to refer to straight or branched chain, saturated or unsaturated hydrocarbon groups having from one to 6, preferably one to 4 carbon atoms. Such groups include alkyl, alkenyl and alkynyl groups of appropriate lengths, and preferably are alkyl, e.g. methyl, ethyl, propyl, butyl, pentyl, or hexyl, or an isomeric form thereof.

[0025] The definition of R may include a cyclic component, $-(CH_2)_mR_1$, wherein m is 0-10, R_2 is an aliphatic ring from about 3 to 7 carbon atoms, or an aromatic or heteroaromatic ring. The "aliphatic ring" may be saturated or unsaturated, and preferably is a saturated ring having 3-7 carbon atoms, inclusive. As an aromatic ring, R_1 preferably is phenyl, and the heteroaromatic rings have oxygen, nitrogen or sulfur as a heteroatom, i.e., R_1 may be thienyl, furanyl, pyridyl, etc. Preferably m is 0-4.

[0026] Preferred representatives of the compounds within the scope of the present invention are (±) trans-2-[-4(1-hydroxyhexyl)phenyl]-5-oxocyclopentaneheptanoicacid, unsaturated derivatives thereof, and lower alkyl esters of these

compounds.

[0027] The following compound may be used in the pharmaceutical compositions and the methods of treatment of the present invention are (±) trans-2-[-4(1-hydroxyhexyl) phenyl]-5-oxocyclopentaneheptanoicacid.

[0028] A pharmaceutically acceptable salt is any salt which retains the activity of the parent compound and does not impart any deleterious or undesirable effect on the subject to whom it is administered and in the context in which it is administered. Such salts are those formed with pharmaceutically acceptable cations, e.g., alkali metals, alkali earth metals, etc.

[0029] Pharmaceutical compositions may be prepared by combining a therapeutically effective amount of at least one compound according to the present invention, or a pharmaceutically acceptable salt thereof, as an active ingredient, with conventional ophthalmically acceptable pharmaceutical excipients, and by preparation of unit dosage forms suitable for topical ocular use. The therapeutically efficient amount typically is between about 0.0001 and about 5% (w/v), preferably about 0.001 to about 1.0% (w/v) in liquid formulations.

[0030] For ophthalmic application, preferably solutions are prepared using a physiological saline solution as a major vehicle. The pH of such ophthalmic solutions should preferably be maintained between 4.5 and 8.0 with an appropriate buffer system, a neutral pH being preferred but not essential. The formulations may also contain conventional, pharmaceutically acceptable preservatives, stabilizers and surfactants.

[0031] Preferred preservatives that may be used in the pharmaceutical compositions of the present invention include, but are not limited to, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate and phenylmercuric nitrate. A preferred surfactant is, for example, Tween 80. Likewise, various preferred vehicles may be used in the ophthalmic preparations of the present invention. These vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose cyclodextrin and purified water.

[0032] Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium chloride, mannitol and glycerin, or any other suitable ophthalmically acceptable tonicity adjustor.

[0033] Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmically acceptable. Accordingly, buffers include acetate buffers, citrate buffers, phosphate buffers and borate buffers. Acids or bases may be used to adjust the pH of these formulations as needed.

[0034] In a similar vein, an ophthalmically acceptable antioxidant for use in the present invention includes, but is not limited to, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole and butylated hydroxytoluene.

[0035] Other excipient components which may be included in the ophthalmic preparations are chelating agents. The preferred chelating agent is edentate disodium, although other chelating agents may also be used in place of or in conjunction with it.

[0036] The ingredients are usually used in the following amounts:

Ingredient	Amount (% w/v)
active ingredient	about 0.001-5
preservative	0-0.10
vehicle	0-40
tonicity adjustor	0-10
buffer	0.01-10
pH adjustor	q.s. pH 4.5-8.0
antioxidant	as needed
surfactant	as needed
purified water	as needed to make 100%

[0037] The actual dose of the active compounds of the present invention depends on the specific compound, and on the condition to be treated; the selection of the appropriate dose is well within the knowledge of the skilled artisan.

[0038] The ophthalmic formulations of the present invention are conveniently packaged in forms suitable for metered application, such as in containers equipped with a dropper, to facilitate application to the eye. Containers suitable for dropwise application are usually made of suitable inert, nontoxic plastic material, and generally contain between about 0.5 and about 15 ml solution. One package may contain one or more unit doses.

[0039] Especially preservative-free solutions are often formulated in non-resealable containers containing up to about ten, preferably up to about five units doses, where a typical unit dose is from one to about 8 drops, preferably one to about 3 drops. The volume of one drop usually is about 20-35 µl.

[0040] The invention is further illustrated by the following nonlimiting Examples.

Example 1

(±) TRANS-2-[-4(1-HYDROXYHEXYL) PHENYL]-5-OXOCYCLO- PENTANEHEPTANOICACID AND LOWER ALKYL ESTERS THEREOF

[0041] The above acid compound is well known and may be purchased or synthesized by methods known in the art. The lower alkyl esters of this compound may be made by the esterification procedures described in the various patent applications described in the Background of the Invention.

Example 2

Intraocular Pressure

[0042] Intraocular pressure was measured by pneumatonometry in normal monkeys. Studies were performed in conscious animals trained to accept pneumatonometry. The compound of Example 1 was administered topically to one eye in a 25 µl volume drop, the contralateral eye received vehicle as a control. Statistical analysis was by Student's paired t test.

[0043] The intraocular pressure results are summarized in Table 1.

TABLE 1.

EFFECT OF (±) TRANS-2-[-4(1- HYDROXYHEXYL) PHENYL]-5-OXOCYCLO PENTANE HEPTANOIC ACID, 0.1%, B.I.D. ON THE INTRAOCULAR PRESSURE OF NORMAL MONKEYS	
TIME(HR) RELATIVE TO FIRST DOSE	**NET CHANGE IN PRESSURE(MMHg)**
0	**0**
2	**-1.17**
4	**-2.0**
6	**-1.50**
24	**-0.67**
26	**-1.0**
28	**-1.83**
30	**-1.50**
48	**-1.50**
50	**-2.33**
52	**-1.50**
54	**-1.50**
72	**-2.33**
74	**-2.17**
76	**-2.33**
78	**-2.0**
96	**-1.83**
98	**-2.0**
100	**-2.0**
102	**-2.0**
(all changes in intraocular pressure are significant $p < 0.01$ according to Students t test)	

Example 3

Intraocular Pressure Reduction After Laser Treatment

[0044] Intraocular pressure reduction was also achieved in laser-induced ocular hypertensive monkeys. Ocular hypertension was induced by photocoagulating the trabecular meshwork by circumferential argon laser treatment.

TABLE 2.

EFFECT OF A SINGLE DOSE (0.1%) OF TRANS- 2-[-4(1-HYDROXYHEXYL)PHENYL]-5-OXO-CYCLOPENTANEHEPTANOIC ACID ON OCULAR PRESSURE ON LASER-INDUCED OCULAR HYPERTENSIVE MONKEYS	
TIME (HR) RELATIVE TO FIRST DOSE	**CHANGE IN INTRA- OCULAR PRESSURE (MMHg)**
0	0
1	-4.5**
2	-6.0**
4	-4.7**
6	-4.5*

* $p<0.05$

** $p < 0.01$ (Students t test)

Example 4

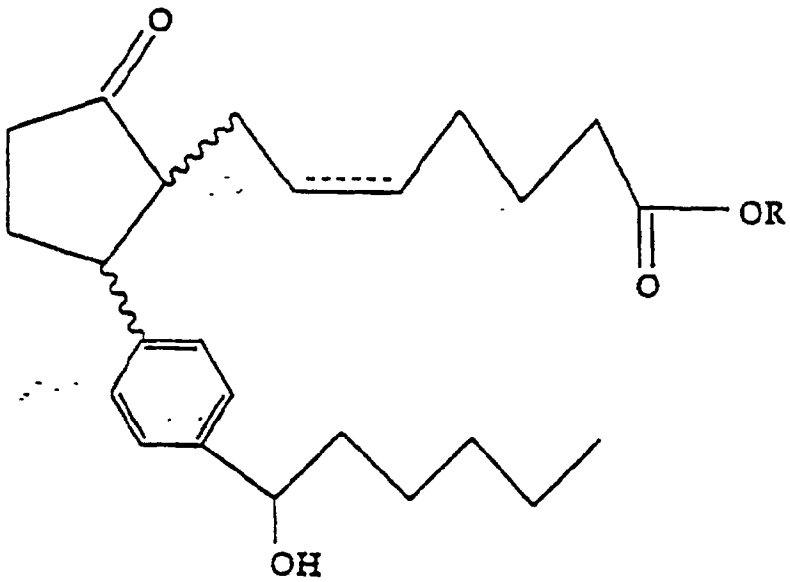
Determination of EP_2 Receptor Activity

[0045] EP_2 receptor activity may be measured in accordance with the procedure disclosed in Woodward et al, Prostaglandins, pp. 371-383, 1993, which is hereby incorporated by reference in its entirety.

[0046] The foregoing description details specific methods and compositions that can be employed to practice the present invention, and represents the best mode contemplated. However, it is apparent from one of ordinary skill in the art that different pharmaceutical compositions may be prepared and used with substantially the same results. That is other EP_2-receptor agonists, such as 19R(OH)PGE_2, butaprost, etc. will effectively lower intraocular pressure in animals and are within the broad scope of the present invention.

Claims

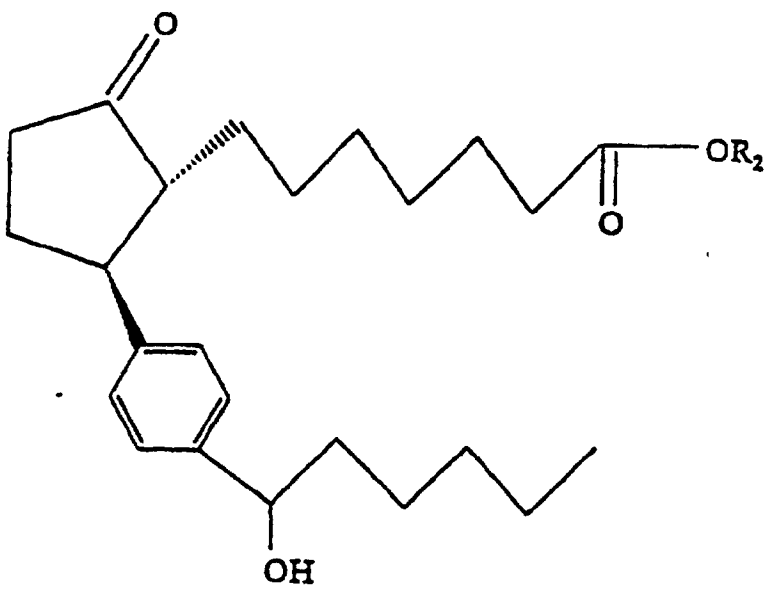
1. A compound for use in treating ocular hypertension the compound being of the formula I



wherein the wavy bonds indicate that α or β configuration, the dashed bond represents either a single or double bond, which double bond may be a cis or trans double bond and R is a saturated or unsaturated acyclic hydrocarbon group having from 1 to 20 carbon atoms, or-$(CH_2)_mR_1$ wherein m is 0-10, and R_1 is an aliphatic ring having from 3 to 7 carbon atoms, or an aryl or heteroaryl ring having from 4 to 10 carbon atoms and wherein the

heteroatom is selected from the group consisting of N, O and S.

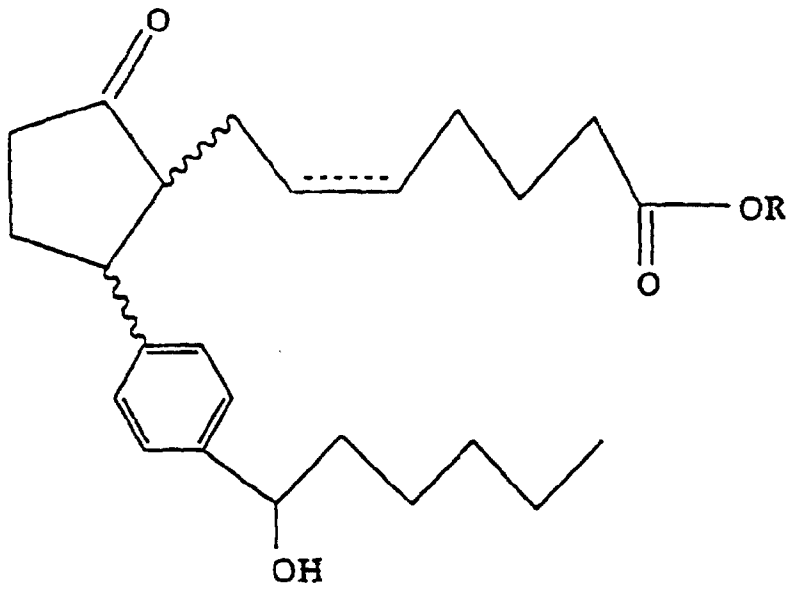
2. The compound of Claim 1 which is a prostaglandin derivative of the formula II



wherein R_2 is a C_{1-5} alkyl radical, the hatched line indicates the α configuration and the solid triangular line indicates the β configuration.

3. A compound for use in treating ocular hypertension, wherein said compound is (±) trans-2-[-4(1-hydroxyhexyl) phenyl]-5-oxocyclopentane-heptanoicacid.

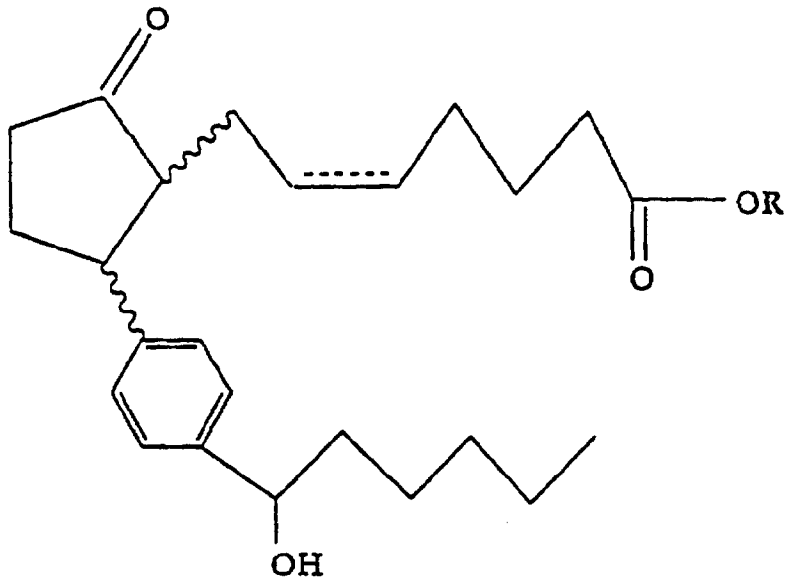
4. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I



wherein the wavy bonds indicate that α or β configuration, the dashed bond represents either a single or double bond, which double bond may be a cis or trans double bond and R is a saturated or unsaturated acyclic hydrocarbon

group having from 1 to 20 carbon atoms, or -$(CH_2)_mR_1$ wherein m is 0-10, and R_1 is an aliphatic ring having from 3 to 7 carbon atoms, or an aryl or heteroaryl ring having from 4 to 10 carbon atoms and wherein the heteroatom is selected from the group consisting of N, O and S.

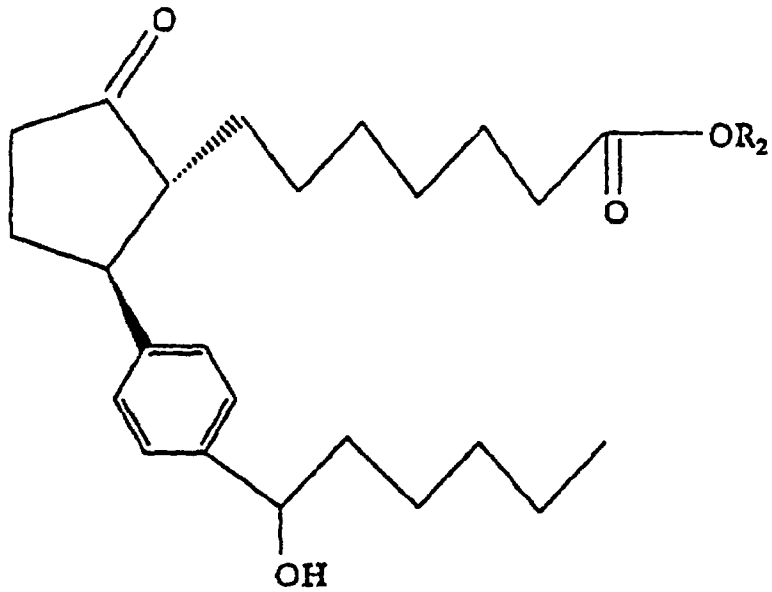
5. An ophthalmic solution comprising a therapeutically effective amount of a compound of formula I



wherein the wavy bonds indicate that α or β configuration, the dashed bond represents either a single or double bond, which double bond may be a cis or trans double bond and R is a saturated or unsaturated acyclic hydrocarbon group having from 1 to 20 carbon atoms, or -$(CH_2)_mR_1$ wherein m is 0-10, and R_1 is an aliphatic ring having from about 3 to 7 carbon atoms, or an aryl or heteroaryl ring having from 4 to 10 carbon atoms and wherein the heteroatom is selected from the group consisting of N, O and S.

6. The ophthalmic solution of Claim 5 comprising at least one ingredient selected from the group of an ophthalmically acceptable preservative, buffer system, antioxidant and chelating agent.

7. The ophthalmic solution of Claim 6 wherein said compound is a prostaglandin derivative of the formula II



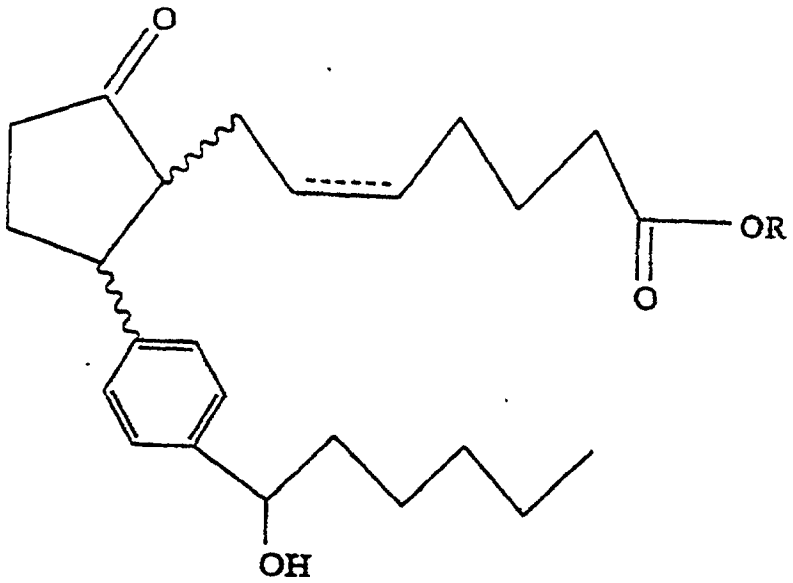
wherein R_2 is a C_{1-5} alkyl radical, the hatched line indicates the α configuration and the solid triangular line indicates the β configuration.

8. An ophthalmic solution comprising a therapeutically effective amount of (±) trans-2-[-4(1-hydroxyhexyl) phenyl]-5-oxocyclopentaneheptanoicacid, and ester and unsaturated derivatives thereof.

9. A pharmaceutical product, comprising

a container adapted to dispense its contents in metered form; and
an ophthalmic solution therein, as defined in. Claim 5.

10. A compound of the formula I



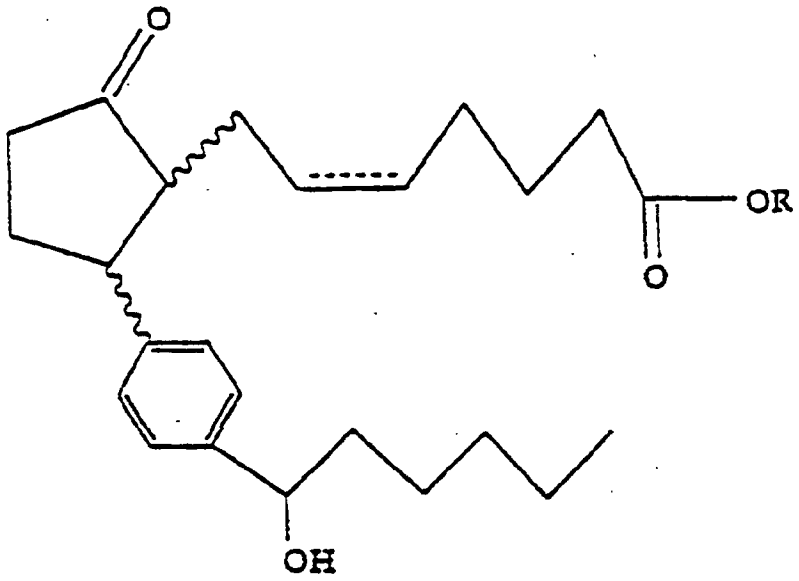
wherein the wavy bonds indicate that α or β configuration, the dashed bond represents either a single or double bond, which double bond may be a cis or trans double bond and R is a saturated or unsaturated acyclic hydrocarbon group having from 1 to 20 carbon atoms, or - $(CH_2)_mR_1$ wherein m is 0-10, and R_1 is an aliphatic ring having from about 3 to 7 carbon atoms, or an aryl or heteroaryl ring having from 4 to 10 carbon atoms and wherein the heteroatom is selected from the group consisting of N, O and S.

11. The use of a compound having EP_2 receptor agonist activity for the manufacture of a medicament for treating ocular hypertension, said compound not being PGE_2 or a C_{1-5} alkyl ester thereof.

12. The use of a compound as defined in any one of claims 1 to 3 for the manufacture of a medicament for treating ocular hypertension.

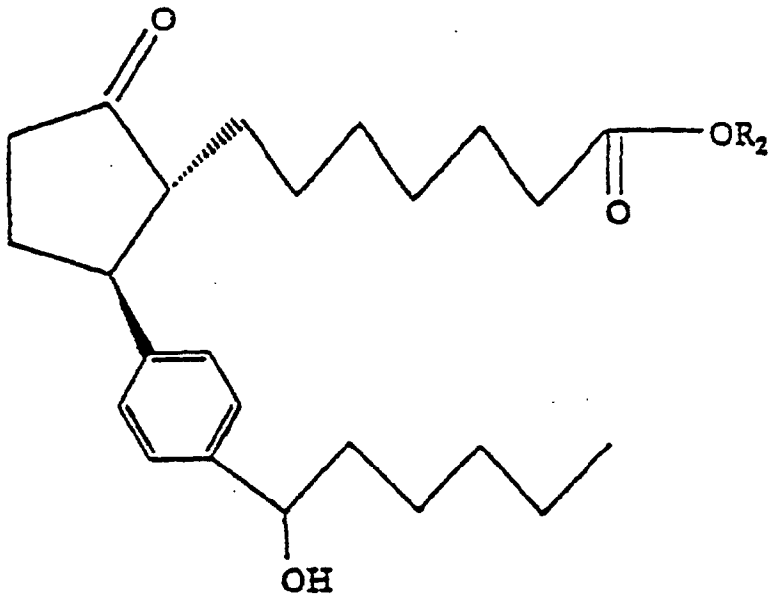
Patentansprüche

1. Verbindung zur Verwendung bei der Behandlung der okularen Hypertension, wobei die Verbindung die Formel I ist



bei der die gewellten Bindungen eine α- oder β-Konfiguration anzeigen, bei der die gestrichelte Bindung entweder eine Einfach- oder Doppelbindung anzeigt, wobei die Doppelbindung eine cis- oder trans-Doppelbindung sein kann und R eine gesättigte oder ungesättigte azyklische Kohlenwasserstoff-Gruppe mit 1 bis 20 Kohlenstoffatomen, oder $-(CH_2)_mR_1$ ist, wobei m 0 - 10 ist und R_1 ein aliphatischer Ring mit von 3 bis 7 Kohlenstoffatomen oder ein Aryl- oder Heteroarylring mit von 4 bis 10 Kohlenstoffatomen ist, und bei der das Heteroatom aus der Gruppe ausgewählt ist, die aus N, O und S besteht.

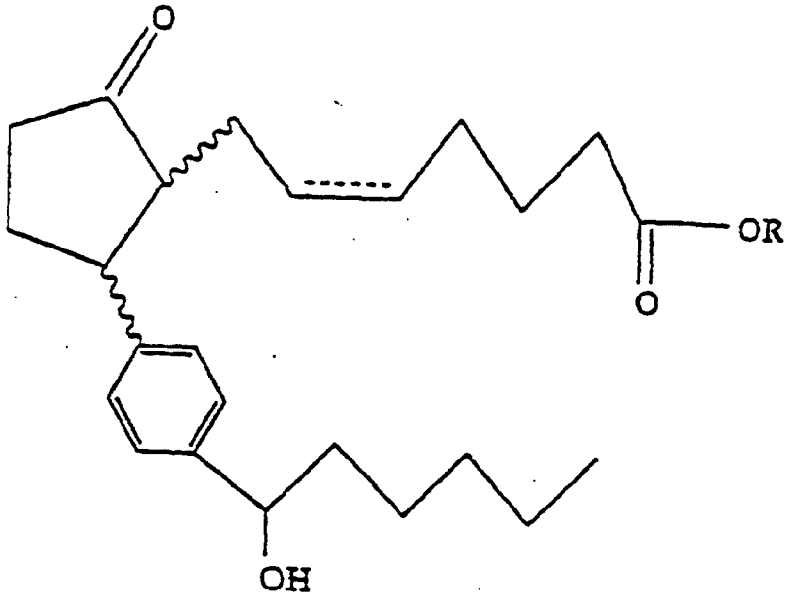
2. Verbindung nach Anspruch 1,
die ein Prostaglandin-Derivat der Formel II ist



bei der R_2 ein C_{1-5}-Alkylradikal ist, wobei die schraffierte Linie die α-Konfiguration und die ausgefüllte dreieckige Linie die β-Konfiguration anzeigt.

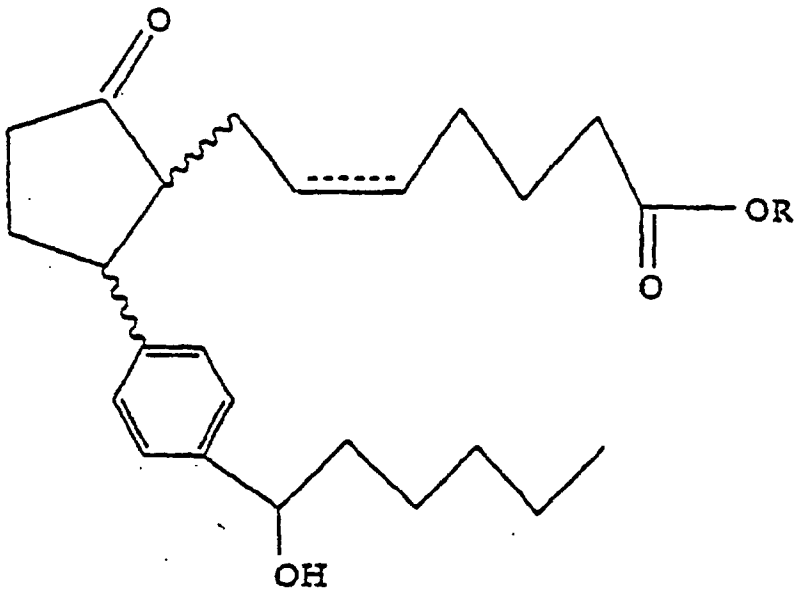
3. Verbindung zur Verwendung in der Behandlung der okularen Hypertension,
wobei die Verbindung (±) trans-2-[-4(1-Hydroxyhexyl)phenyl]-5-oxocyclopentan-heptansäure ist.

4. Pharmazeutische Zusammensetzung,
die eine therapeutisch wirksame Menge einer Verbindung nach Formel 1 umfaßt



bei der die gewellten Bindungen eine α- oder β-Konfiguration anzeigen, wobei die gestrichelte Bindung entweder eine Einfach- oder Doppel-Bindung repräsentiert, wobei die Doppelbindung eine cis- oder trans-Dopppelbindung sein kann und R eine gesättigte oder ungesättigte azyklische Kohlenwasserstoffgruppe mit von 1 bis 20 Kohlenstoffatomen ist oder $-(CH_2)_mR_1$, wobei m 0 - 10 ist und R_1 ein aliphatischer Ring mit von 3 bis 7 Kohlenstoffatomen oder ein Aryl- oder Heteroarylring mit von 4 - 10 Kohlenstoffatomen ist, und wobei das Heteroatom aus der Gruppe ausgewählt ist, die aus N, O und S besteht.

5. Ophthalmische Lösung,
die eine therapeutisch wirksame Menge einer Verbindung der Formel I

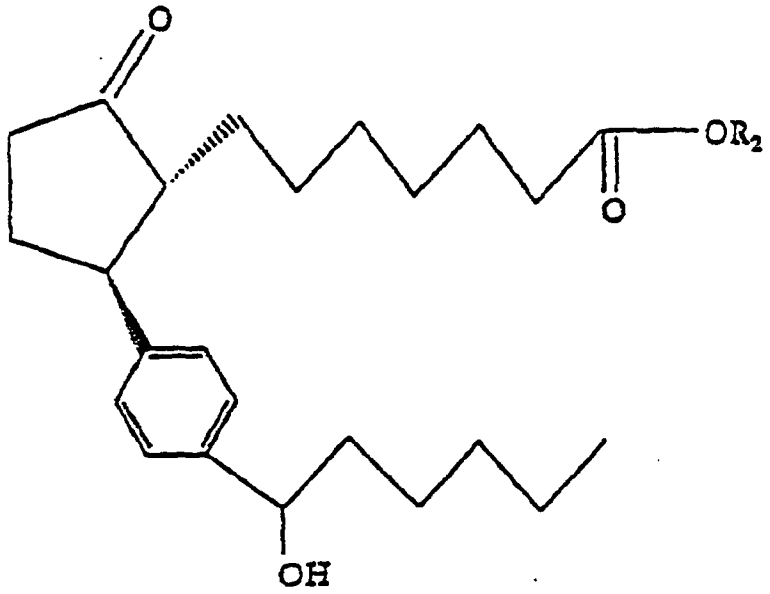


umfaßt,
wobei die gewellten Bindungen eine α- oder β-Konfiguration anzeigen, wobei die gestrichelte Linie entweder eine

Einfach- oder Doppel-Bindung repräsentiert, wobei die Doppelbindung eine cis- oder trans-Dopppelbindung sein kann und R eine gesättigte oder ungesättigte azyklische Kohlenwasserstoffgruppe mit von 1 bis 20 Kohlenstoffatomen ist oder $-(CH_2)_mR_1$, wobei m 0 - 10 ist und R_1 ein aliphatischer Ring mit von ungefähr 3 bis 7 Kohlenstoffatomen oder ein Aryl- oder Heteroarylring mit von 4 - 10 Kohlenstoffatomen ist, und bei der das Heteroatom aus der Gruppe ausgewählt ist, die aus N, O und S besteht.

6. Ophthalmische Lösung nach Anspruch 5,
die zumindest einen Inhaltsstoff umfaßt, der aus der Gruppe eines ophthalmisch akzeptablen Konservierungsmittels, Puffersystems, Antioxidans und Komplexbildners ausgewählt ist.

7. Ophthalmische Lösung nach Anspruch 6,
bei der die Verbindung ein Prostaglandinderivat der Formel II ist

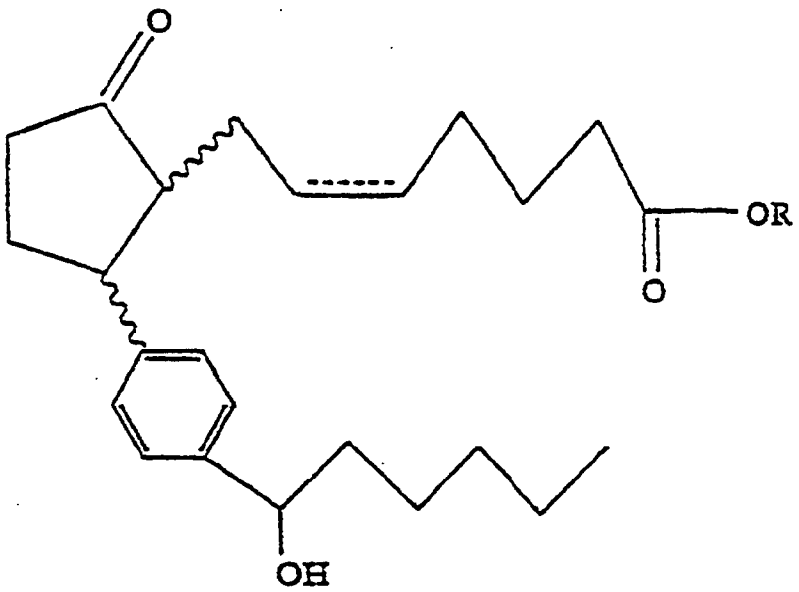


bei der R_2 ein C_{1-5} Alkylradikal ist, wobei die schraffierte Linie die α-Konfiguration anzeigt und die ausgefüllte dreieckige Linie die β-Konfiguration anzeigt.

8. Ophthalmische Lösung,
die eine therapeutisch wirksame Menge von (±) trans-2-[-4(1-Hydroxyhexyl)phenyl]-5-oxocyclopentanheptansäure und Ester und ungesättigte Derivate hiervon, umfaßt.

9. Pharmazeutisches Produkt,
das einen zur Abgabe dessen Inhalts in abgemessener Form angepaßten Behälter; und darin eine ophthalmische Lösung umfaßt, wie sie in Anspruch 5 definiert ist.

10. Verbindung der Formel I



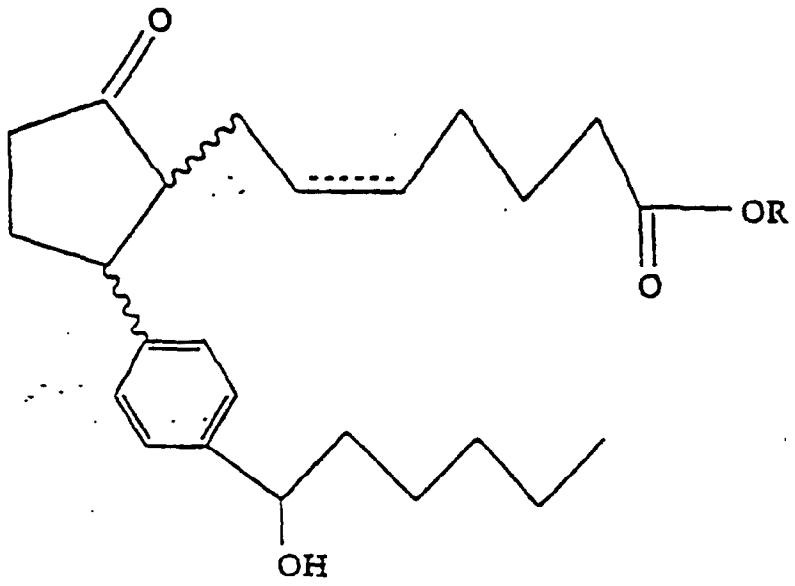
bei der die gewellten Bindungen die α- oder β-Konfiguration anzeigen, wobei die gestrichelte Linie entweder eine Einfach- oder Doppel-Bindung anzeigt, wobei die Doppelbindung eine cis- oder trans-Dopppelbindung sein kann und R eine gesättigte oder ungesättigte azyklische Kohlenwasserstoffgruppe mit von 1 bis 20 Kohlenstoffatomen oder $-(CH_2)_mR_1$ ist, wobei m 0 - 10 ist und R_1 ein aliphatischer Ring mit von ungefähr 3 bis 7 Kohlenstoffatomen oder ein Aryl- oder Heteroarylring mit von 4 - 10 Kohlenstoffatomen ist, und wobei das Heteroatom aus der Gruppe ausgewählt ist, die aus N, O und S besteht.

11. Verwendung einer Verbindung mit einer EP_2-Rezeptor-Agonisten-Aktivität, zur Herstellung eines Medikaments zur Behandlung der okularen Hypertension, wobei die Verbindung nicht PGE_2 oder ein C_{1-5} Alkylester hiervon ist.

12. Verwendung einer wie in einem der Ansprüche 1 bis 3 definierten Verbindung zur Herstellung eines Medikaments zur Behandlung der okularen Hypertension.

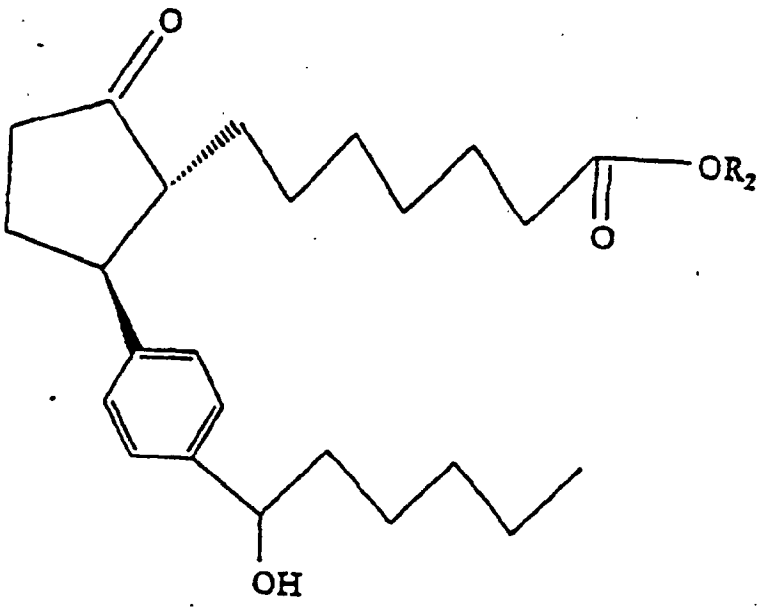
Revendications

1. Composé pour une utilisation dans le traitement de l'hypertension oculaire, le composé ayant la formule I



dans laquelle les liaisons ondulées indiquent une configuration en α ou β, la liaison en pointillés représente soit une liaison simple ou double, laquelle double liaison peut être une liaison double cis ou trans et R est un groupe hydrocarbure acyclique saturé ou non saturé possédant de 1 à 20 atomes de carbone, ou $-(CH_2)_mR_1$ dans lequel m est 0-10, et R_1 est un anneau aliphatique possédant de 3 à 7 atomes de carbone, ou un anneau aryle ou hétéroaryle possédant de 4 à 10 atomes de carbone et dans lequel l'hétéroatome est choisi parmi le groupe consistant en N, O et S.

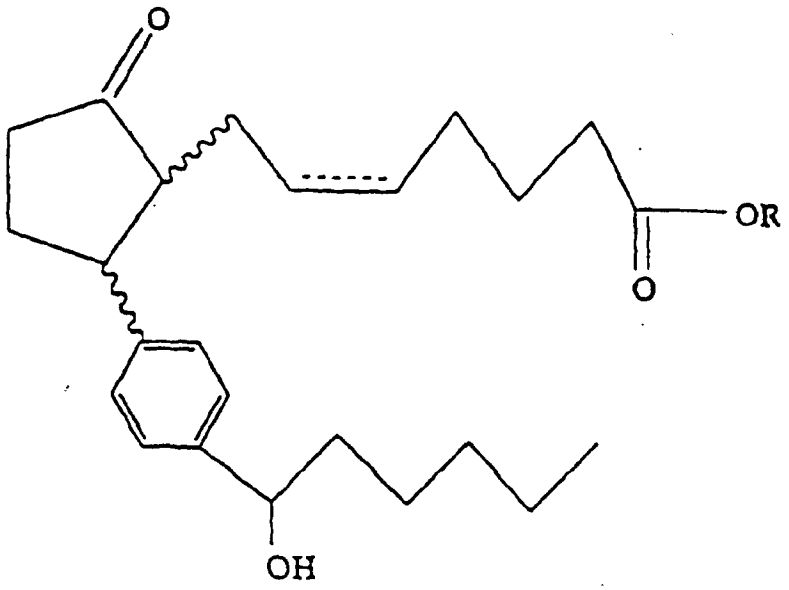
2. Composé selon la revendication 1 qui est un dérivé d'une prostaglandine de formule II



dans laquelle R_2 est un radical alkyle en C_{1-5}, la ligne hachurée indique une configuration en α et la ligne triangulaire en trait plein indique une configuration en β.

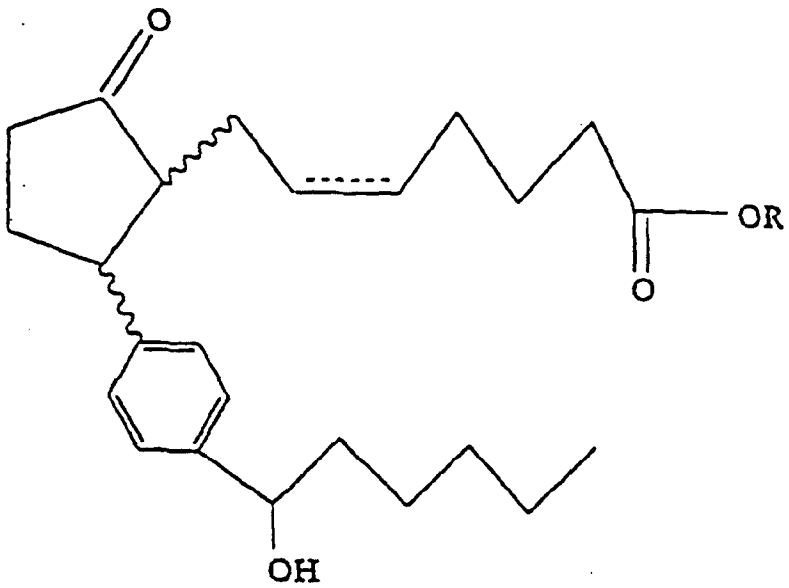
3. Un composé pour une utilisation dans le traitement de l'hypertension oculaire, dans lequel ce composé est l'acide (±) trans-2-[-4(1-hydroxyhexyl)phényl]-5-oxocyclopentane-heptanoïque.

4. Composition pharmaceutique comprenant une quantité thérapeutiquement efficace d'un composé de formule I



dans laquelle les liaisons ondulés indiquent une configuration en α ou en β, la liaison en pointillés représente soit une liaison simple ou double, laquelle double liaison peut être une liaison double en cis ou trans et R est un groupe hydrocarbure acyclique saturé ou non saturé possédant de 1 à 20 atomes de carbone, ou $-(CH_2)_mR_1$ dans lequel m est 0-10, et R_1 est un anneau aliphatique possédant de 3 à 7 atomes de carbone, ou un anneau aryle ou hétéroaryle possédant de 4 à 10 atomes de carbone et dans lequel l'hétéroatome est choisi parmi le groupe consistant en N, O et S.

5. Une solution ophtalmologique comprenant une quantité thérapeutiquement efficace d'un composé de formule I

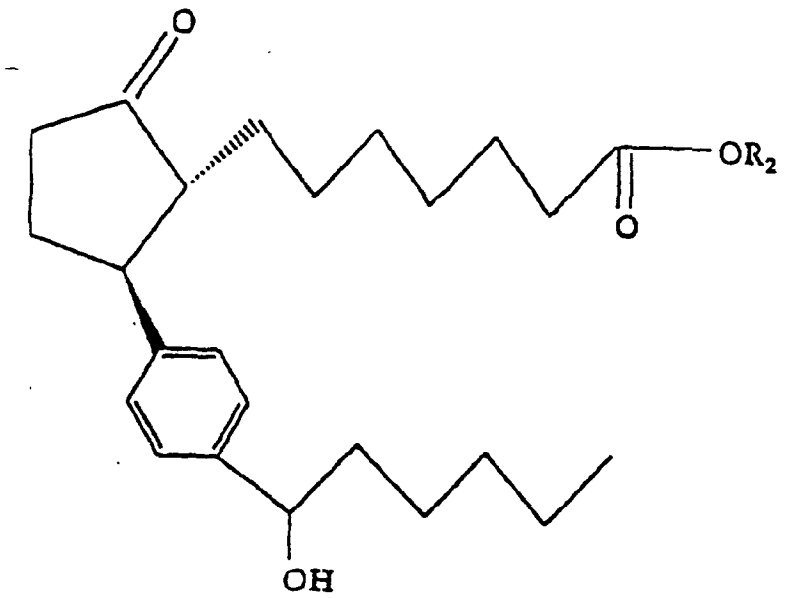


dans laquelle les liaisons ondulées indiquent une configuration α ou β, la liaison en pointillés représente soit une liaison simple ou double, laquelle double liaison peut être une liaison double en cis ou trans et R est un groupe hydrocarbure acyclique saturé ou non saturé possédant de 1 à 20 atomes de carbone, ou $-(CH_2)_mR_1$ dans lequel m est 0-10, et R_1 est un anneau aliphatique groupe hydrocarbure acyclique saturé ou non saturé possédant de 1

à 20 atomes de carbone, ou $-(CH_2)_mR_1$ dans lequel m est 0-10, et R_1 est un anneau aliphatique possédant environ 3 à 7 atomes de carbone, ou un anneau aryle ou hétéroaryle possédant de 4 à 10 atomes de carbone et dans lequel l'hétéroatome est choisi parmi le groupe consistant en N, O et S.

6. Solution ophtalmologique selon la revendication 5 comprenant au moins un ingrédient choisi parmi le groupe d'un conservateur ophtalmologiquement acceptable, un système tampon, un antioxydant et un agent chélateur.

7. Solution ophtalmologique selon la revendication 6 dans laquelle ce composé est un dérivé d'une prostaglandine de formule II



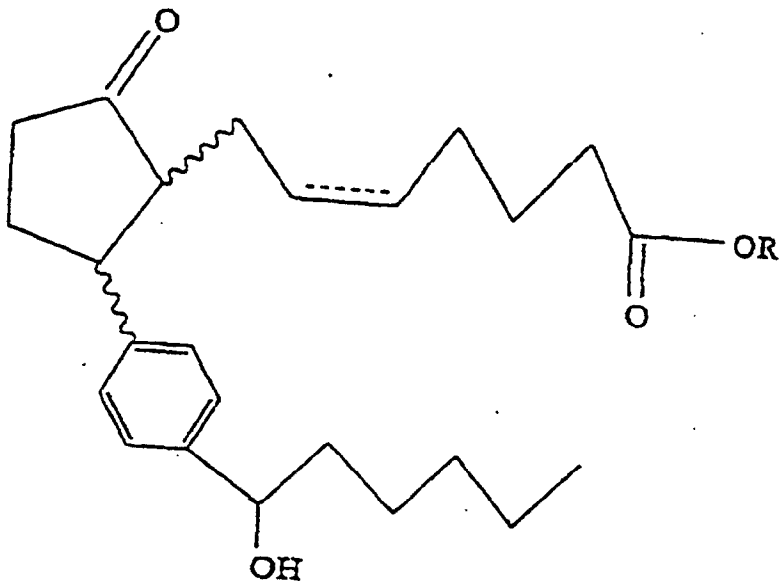
dans laquelle R_2 est un radical alkyle en C_{1-5}, la ligne hachurée indique une configuration en α et la ligne triangulaire solide indique une configuration en β.

8. Solution ophtalmologique comprenant une quantité thérapeutiquement efficace de l'acide (±) trans-2-[-4(1-hydroxyhexyl)phényl]-5-oxocyclopentaneheptanoïque, et ester et des dérivés non saturés de celui-ci.

9. Produit pharmaceutique, comprenant

un conteneur conçu pour diffuser son contenu sous forme dosée; et
une solution ophtalmologique dans celui-ci, telle que définie dans la revendication 5.

10. Composé de formule I



dans laquelle les liaisons ondulées indiquent une configuration en α ou β, la liaison en pointillés représente soit une liaison simple ou double, laquelle double liaison peut être une liaison double en cis ou trans et R est un groupe hydrocarbure acyclique saturé ou non saturé possédant de 1 à 20 atomes de carbone, ou $-(CH_2)_mR_1$ dans lequel m est 0-10, et R_1 est un anneau aliphatique possédant d'environ 3 à 7 atomes de carbone, ou un anneau aryle ou hétéroaryle possédant de 4 à 10 atomes de carbone et dans lequel l'hétéroatome est choisi parmi le groupe consistant en N, O et S.

11. Utilisation d'un composé possédant une activité agoniste du récepteur EP_2 pour la fabrication d'un médicament pour le traitement de l'hypertension oculaire, ce composé n'étant pas un PGE_2 ou un alkyle ester en C_{1-5} de celui-ci.

12. Utilisation d'un composé tel que défini dans l'une quelconque des revendications 1 à 3 pour la fabrication d'un médicament pour le traitement de l'hypertension oculaire.